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10/081,126	02/22/2002	Gerald W. DeVries	P-AR 4951	8539

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CATHRYN CAMPBELL
CAMPBELL & FLORES LLP
7th Floor
4370 La Jolla Village Drive
San Diego, CA 92122

EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) 2-7, 11-14 and 16-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 8-10, 15 and 26-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 February 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO 802)

DETAILED ACTION

1. Claims 1-38 are pending.
2. Applicant's election without traverse of Group III, claims 1, 8-11, 15 and 26-38, now drawn to (claims 1, 8-10, 15 and 26-38) drawn to a method of extending corneal graft survival comprising administering a VEGF receptor (VEGFR-3) inhibitor wherein the inhibitor is a VEGFR-3 kinase inhibitor, filed 3/1/04, is acknowledged. Claim 11 was inadvertently included in Group III in the restriction mailed 2/13/04.
3. Claims 2-7, 11-14 and 16-25 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 1, 8-10, 15 and 26-38 are being acted upon in this Office Action.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 1, 8-10, 15 and 26-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of extending of extending corneal graft survival following corneal transplantation in a patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising 3(2,4-dihydroxy-benzylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one (MAE106) or 3-(4-dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51), **does not** reasonably provide enablement for (1) a method of extending corneal graft survival following corneal transplantation in a patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising *any* "vascular endothelial growth receptor-3 (VEGFR-3) inhibitor", *any* "VEGFR-3 kinase inhibitor", *any* "ATP analog", *any* "VEGFR-3 binding molecule", *any* "VEGFR-3 inhibitor down regulates VEGFR-3 expression", (2) the method mentioned above further comprising administering to said patient *any* "anti-angiogenic

administered prior to, or subsequent to corneal transplantation, two or more times, over a period of at least one or six months as set forth in claims 1, 8-11, 15 and 26-32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benzylidene)-1,3-dihydroindol-2-one (MAE87), 3-(3-(fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one (MAE106) or 3-(4-dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structures as shown on page 56 and a method of extending corneal graft survival in a rat model of keratoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benzylidene)-1,3-dihydroindol-2-one (MAE87), 3-(3-(fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one (MAE106) or 3-(4-dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51).

The specification does not teach how to make *any* "vascular endothelial growth receptor-3 (VEGFR-3) inhibitor", *any* "VEGFR-3 kinase inhibitor", *any* "ATP analog", *any* "VEGFR-3 binding molecule", *any* "VEGFR-3 inhibitor down regulates VEGFR-3 expression", *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", much less for extending corneal graft survival following corneal transplantation in a patient because the terms "inhibitor", "analog", "agent" do not convey the structure without the amino acid sequence or chemical structure. The claims are drawn to a method of extending corneal graft survival by administering a genus of "vascular endothelial growth receptor-3 (VEGFR-3) inhibitor", "VEGFR-3 kinase inhibitor", "ATP analog", "VEGFR-3 binding molecule", "VEGFR-3 inhibitor down regulates VEGFR-3 expression", "anti-angiogenic agent", and "immunosuppressive agent". The specification does not teach how to make any inhibitor mentioned above because there is insufficient guidance as to the structure without the amino acid sequence or chemical structure of any "vascular endothelial

growth receptor-3 (VEGFR-3) inhibitor”, *any* “VEGFR-3 kinase inhibitor”, *any* “ATP analog”, *any* “VEGFR-3 binding molecule”, *any* “VEGFR-3 inhibitor down regulates VEGFR-3 expression”, *any* “anti-angiogenic agent”, or *any* “immunosuppressive agent”, let alone which undisclosed inhibitor binds to VEGFR-3 and function to inhibit lymphangiogenesis, and thereby extending corneal graft survival. Even if the inhibitor binds to VEGFR-3, binding does not equal to inhibiting lymphoangiogenesis, in turn, useful for extending corneal graft survival. Likewise, inhibiting VEGFR-3 expression does not equal to extending corneal graft survival without sufficient working example. Even if the inhibitor binds to VEGFR-3, binding does not necessary mean down regulating VEGFR-3 expression.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the indefinite number of undisclosed VEGFR-3 inhibitor, there is insufficient guidance as to which conformational changes and amino acids contact with the VEGFR-3 are responsible for inhibiting lymphoangiogenesis, ATP binding and/or tyrosine kinase phosphorylation. Further, there is insufficient in vivo working example demonstrating that all VEGFR-3 inhibitor are effective for extending corneal graft survival. Given the indefinite number of undisclosed VEGFR-3 inhibitor, it is unpredictable which undisclosed inhibitor binds and has which particular function such as binding to the VEGFR-3 catalytic domain, down regulating VEGFR-3 expression and/or tyrosine kinase phosphorylation. Until the VEGFR-3 receptor inhibitor has been identified, the specification as filed merely invites one of skill in the art for further experimentation. Since the VEGFR-3 inhibitor, VEGFR-3 kinase inhibitor, and ATP analog in the claimed method are not enabled, it follows that the said method further comprising any undisclosed anti-angiogenic agent, or immunosuppressive agent is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

7. Claims 1, 8-10, 15 and 26-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* “vascular endothelial growth receptor-3 (VEGFR-3) inhibitor”, *any* “VEGFR-3 kinase inhibitor”, *any* “ATP analog”, *any* “VEGFR-3 binding molecule”, *any* “VEGFR-3 inhibitor down regulates VEGFR-3 expression”, *any* “anti-angiogenic agent”, and *any* “immunosuppressive agent” for the claimed method of extending corneal graft as set forth in claims 1, 8-11, 15 and 26-32.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benzylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2-one (MAE106) or 3-(4-dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival in a rat model of keratenoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benzylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2-one (MAE106) or 3-(4-dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51).

The specification defines VEGF-R inhibitor” on page 15, lines 15-21 to mean a molecule that reduces VEGFR-3 expression, activity or intracellular signaling. Such an inhibitor can be a small molecule, protein, peptide, peptidomimetic, ribozyme, nucleic acid molecule or oligonucleotides, cell, phage, virus, oligosaccharide or a combination thereof...without limitation. The specification discloses on page 41 that anti-angiogenic agent include, without limitation, small molecules, proteins such as angiogenic factors and receptors, transcription factors, and antibodies and antigen-binding fragment thereof, peptides, and peptidomimetics, and nucleic acid molecule including ribozymes, antisense oligonucleotides, and nucleic acids. However, the

specific structure of said VEGFR-3 inhibitor, anti-angiogenic agent such as amino acid sequence, nucleotide sequence, and antibody binding specificity are not described.

With the exception of the specific inhibitors of VEGFR-3 for the claimed method of extending corneal graft, there is insufficient written description about the structure associated with function of any inhibitors mentioned above without the specific amino acid sequence or the specific chemical structure, let alone which undisclosed inhibitor binds to VEGFR-3 and has which particular function such as inhibiting tyrosine kinase phosphorylation, or ATP binding activity. Since the VEGFR-3 inhibitor, VEGFR-3 kinase inhibitor, and ATP analog in the claimed method are not enabled, it follows that the said method further comprising any undisclosed anti-angiogenic agent, or immunosuppressive agent is not enabled.

The specification discloses only three specific VEGFR-3 kinase inhibitors that extend corneal graft rejection. Given the lack of any additional species of "vascular endothelial growth receptor-3 (VEGFR-3) inhibitor", "VEGFR-3 kinase inhibitor", "ATP analog", "VEGFR-3 binding molecule", "VEGFR-3 inhibitor down regulates VEGFR-3 expression", "anti-angiogenic agent", and "immunosuppressive agent" for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
10. Claims 1 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbort *et al* (Jpn J Ophthalmol 33(2): 212-20, 1989; PTO 892) in view of Mimura *et al* (Exp Eye Res. 72(1): 71-8, Jan 2001, PTO 1449) and Veikkola *et al* (EMBO J 20(6): 1223-1231, Nov 2001; PTO 1449).

Herbort *et al* teach a method of extending corneal graft survival following corneal transplant comprising administering to a patient such as a rat a pharmaceutical composition comprising Cyclosporin A (CsA). The reference CsA is an immunosuppressive agent that reduces graft neovascularization (See abstract, in particular).

The claimed invention in claim 1 differs from the reference only that the method of extending corneal graft by administering a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor instead of CsA subsequent to corneal transplantation.

Mimura *et al* teach lymphatic vessels may contribute to a decrease success rate of keratoplasty in vascularized cornea by accelerating antigen recognition and graft rejection. The VEGF-R in the cornea is minimally detected before the injury and is up-regulate 3 and 7 days after the injury in several new vessels in the corneal stroma. Both VEGF-C and VEGFR-3 play a role in corneal lymphangiogenesis (See abstract, in particular).

Veikkola *et al* teach that growth of new blood and lymphatic vessels requires VEGF-C or VEGF-D binding to VEGFR-3. Signaling via vascular endothelial growth factor receptor-3 (VEGFR-3) is sufficient for lymphangiogenesis and stimulation of VEGFR-3 by ligand-C156S is sufficient for generating the hyperplastic lymphatic phenotype (See abstract, page 1224, column 1, 1st paragraph, in particular). Veikkola *et al* further teach that administering VEGFR-3 inhibitor such as soluble VEGFR-3 is capable of blocking VEGF-D and VEGF-C 156S induced lymphatic hyperplasia in vivo (See page 1228, Figure 7, column 2, second paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cyclosporine A in the pharmaceutical composition for a

method of extending corneal graft survival as taught by Herbort et al for the VEGFR-3 inhibitor such as soluble VEGFR-3 as taught by Veikkola et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Herbort et al teach that graft neovascularization is responsible for corneal graft failure and corneal graft survival following corneal transplant can be extended by administering Cyclosporin A (CsA). Mimura *et al* teach lymphatic vessels may contribute to a decrease success rate of keratoplasty in vascularized cornea by accelerating antigen recognition and graft rejection. The VEGFR-3 in the cornea is minimally detected before the injury and is up-regulated 3 and 7 days after the injury in several new vessels in the corneal stroma. Both VEGF-C and VEGFR-3 play a role in corneal lymphangiogenesis (See abstract, in particular). Veikkola *et al* teach that signaling via vascular endothelial growth factor receptor is sufficient for lymphangiogenesis and stimulation of VEGFR-3 and administering soluble VEGFR-3 is capable of blocking VEGF-D and VEGF-C 156S induced lymphatic hyperplasia in vivo (See page 1228, Figure 7, column 2, second paragraph, in particular).

11. Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbort *et al* (Jpn J Ophthalmol 33(2): 212-20, 1989; PTO 892) in view of Mimura *et al* (Exp Eye Res. 72(1): 71-8, Jan 2001, PTO 1449) and Veikkola *et al* (EMBO J 20(6): 1223-1231, Nov 2001; PTO 1449) as applied to claims 1 and 29 and further in view of Kirkin *et al* (Eur J Biochem 268: 5530-5540, 2001; PTO 1449).

The combined teachings of Herbort *et al*, Mimura *et al*, and Veikkola *et al* have been discussed supra.

The claimed invention in claim 8 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by administering a vascular endothelial growth factor receptor-3 (VEGFR-3) kinase inhibitor instead of CsA.

The claimed invention in claim 9 differs from the combined teachings of the references only that the method wherein the vascular endothelial growth factor receptor-3 (VEGFR-3) kinase inhibitor binds to VEGFR-3 catalytic domain.

The claimed invention in claim 10 differs from the combined teachings of the references only that the method wherein the vascular endothelial growth factor receptor-3 (VEGFR-3) kinase inhibitor is an ATP analog.

Kirkin *et al* teach vascular endothelial growth factor receptor-3 (VEGFR-3) kinase inhibitor such as MAE87, MAE106 and MAZ51 which are tyrosine kinase inhibitors that bind to the VEGFR-3 catalytic domain and block VEGFR-3 kinase activity (See Figures 5 & 6, page 5536, column 2, 3rd paragraph, in particular). The reference VEGFR-3 kinase inhibitors are ATP analog which mimic and compete with ATP binding (see page 5538, column 1, 2nd paragraph, in particular). Kirkin *et al* teach VEGFR-3 specific kinase inhibitors are useful for inhibiting VEGF-C and VEGF-D induced activation of VEGFR-3 mediated lymphangiogenesis (See page 5538, column 2, 1st paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cyclosporine A in the method of extending corneal graft survival as taught by Herbort *et al* for the soluble VEGFR-3 as taught by Veikkola *et al* or the VEGFR-3 kinase inhibitor as taught by Kirkin *et al* for a method of extending corneal graft survival following corneal transplantation as taught by Herbort *et al*, Mimura *et al*, Mimura *et al*, Veikkola *et al* and Kirkin *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Herbort *et al* teach that graft neovascularization is responsible for corneal graft failure and corneal graft survival following corneal transplant can be extended by administering Cyclosporin A (CsA). Mimura *et al* teach lymphatic vessels may contribute to a decrease success rate of keratoplasty in vascularized cornea by accelerating antigen recognition and graft rejection. The VEGFR-3 in the cornea is minimally detected before the injury and is up-regulate 3 and 7 days after the injury in several new vessels in the corneal stroma. Both VEGF-C and VEGFR-3 play a role in corneal lymphangiogenesis (See abstract, in particular). Veikkola *et al* teach that signaling via vascular endothelial growth factor receptor via VEGFR-3 is sufficient for lymphangiogenesis and administering a soluble VEGFR-3 is capable of blocking VEGF-D and VEGF-C 156S induced lymphatic hyperplasia in vivo (See page 1228, Figure 7, column 2, second paragraph, in particular). Kirkin *et al* teach VEGFR-3 specific kinase inhibitors are useful for inhibiting

VEGF-C and VEGF-D induced activation of VEGFR-3 mediated lymphangiogenesis (See page 5538, column 2, 1st paragraph, in particular).

12. Claims 26-28, and 30-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbort *et al* (Jpn J Ophthalmol 33(2): 212-20, 1989; PTO 892) in view of Mimura *et al* (Exp Eye Res. 72(1): 71-8, Jan 2001, PTO 1449) and Veikkola *et al* (EMBO J 20(6): 1223-1231, Nov 2001; PTO 1449) as applied to claims 1 and 29 and further in view of Yamagami *et al* (Transplantation 64(1): 42-48, July 1997), Hikita *et al* (Invest Ophthalmol Vis Sci 38(5): 901-9, April 1997; PTO 892) and US Pat 6,331,313 B1 (Dec 2001, PTO 892).

The combined teachings of Herbort *et al*, Mimura *et al*, and Veikkola *et al* have been discussed supra.

The claimed invention in claim 26 differs from the combined teachings of the references only that the method further comprising administering to said patient an anti-angiogenic agent.

The claimed invention in claim 27 differs from the combined teachings of the references only that the method further comprising administering to said patient an immunosuppressive agent.

The claimed invention in claim 28 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by administering a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor wherein the pharmaceutical composition is administered prior to corneal transplantation.

The claimed invention in claim 30 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by administering a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor two or more times.

The claimed invention in claim 31 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by repeats administering a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor over a period of at least one month.

The claimed invention in claim 32 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by repeats administering a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor over a period of at least six months.

The claimed invention in claim 33 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by administering a pharmaceutical composition comprising a VEGFR-3 inhibitor two or more times prior to corneal transplantation.

The claimed invention in claims 35 and 37 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by local administration of a pharmaceutical composition comprising a VEGFR-3 inhibitor.

The claimed invention in claim 36 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation by topical administration of a pharmaceutical composition comprising a VEGFR-3 inhibitor.

The claimed invention in claim 38 differs from the combined teachings of the references only that the method of extending corneal graft survival following corneal transplantation wherein said pharmaceutical composition released from an intraocular or periocular implant.

Yamagami *et al* teach a method of extending the corneal graft survival by administering intraperitoneally (systemic administration) a pharmaceutical comprising an anti-LFA-1 mAb and an immunosuppressive agent such as CsA or FK506. Yamagami *et al* teach that single administration of immunosuppressive agent FK506 or anti-FLA-1 mAb was insufficient to prolong survival time. However, a combination of therapy is more effective for prolonging the survival of corneal graft by suppressing complementary xenoantigen-specific antibody production, in addition to IL-2 production in T cells (See page 47, column 1, in particular).

Hikita *et al* teach a method of extending the corneal graft survival by local and topical administering immunosuppressive agent such as FK506 to avoid its systemic side effects such as diarrhea, weight loss, and liver dysfunction (See page 901, column 2, second paragraph, in particular). Hikita *et al* teach that topical FK506 treatment with eye drops are comparable to those obtained with systemic injection of FK506 with fewer side effects, and shows promise as a drug to prevent corneal graft rejection in humans (see page 907, column 1, second paragraph, See abstract, in particular).

The '313 patent teaches a method of delivering a variety of drugs to the eye by implanting a biocompatible device that release drug locally from an intraocular or periocular implant (See entire document, abstract, in particular). The reference method is useful for

delivering a controlled amount of a desired drug constantly over a period of several days, or weeks or even months without interruption (See column 1, line 26-53, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-LFA-1 mAb in the pharmaceutical composition comprising anti-LFA-1 mAb and CsA or FK506 for a method of extending corneal graft survival as taught by Yamagami *et al* for the antiangiogenic agent such as soluble VEGFR-3 as taught by Veikkola *et al* by administering the pharmaceutical composition systemically as taught by Herbert *et al*, or locally or topically as taught by Hikita *et al* or intraocular or periocular implant as taught by the '313 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Yamagami *et al* teach that a combination of therapy is more effective than a single agent for prolonging the survival of corneal graft by suppressing complementary xenoantigen-specific antibody production, in addition to IL-2 production in T cells (See page 47, column 1, in particular). Herbert *et al* teach that graft neovascularization is responsible for corneal graft failure and corneal graft survival following corneal transplant can be extended by administering Cyclosporin A (CsA). Mimura *et al* teach lymphatic vessels may contribute to a decrease success rate of keratoplasty in vascularized cornea by accelerating antigen recognition and graft rejection. The VEGFR-3 in the cornea is minimally detected before the injury and is up-regulate 3 and 7 days after the injury in several new vessels in the corneal stroma. Both VEGF-C and VEGFR-3 play a role in corneal lymphangiogenesis (See abstract, in particular). Veikkola *et al* teach that signaling via vascular endothelial growth factor receptor is sufficient for lymphangiogenesis and stimulation of VEGFR-3 and administering soluble VEGFR-3 is capable of blocking VEGF-D and VEGF-C 156S induced lymphatic hyperplasia in vivo (See page 1228, Figure 7, column 2, second paragraph, in particular). Hikita *et al* teach that topical FK506 treatment with eye drops are comparable to those obtained with systemic injection of FK506 with fewer side effects, and shows promise as a drug to prevent corneal graft rejection in humans (see page 907, column 1, second paragraph, See abstract, in particular). The '313 patent teaches implanting device could delivered a controlled amount of a desired drug constantly over a period of several days, or weeks or even months without interruption (See column 1, line 26-53, in particular). Claims 28 and 30-33 are included in this rejection because the art teaches such

as administering prior to corneal transplant, two or more times over a period of at least one or six months are apparent to any one of those ordinary skill in the pharmaceutical art. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ233; 235 (CCPA 1955). See MPEP § 2144.05 part IIA.

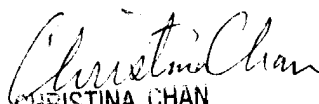
13. No claim is allowed.
14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.
15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

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CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600